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By: _____

PATENT

Atty. Docket No.(TTC): 19904-022-1US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 7228
SCHATZBERG & BELANOFF	Examiner: Brooks, Kristie Latrice
Application No.: 10/519,008	Technical Center/Art Unit: 1609
Filed: December 21, 2004	
For: METHODS FOR TREATING PSYCHOSIS ASSOCIATED WITH INTERFERON-ALPHA THERAPY	DECLARATION OF DR. JOSEPH BELANOFF UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Joseph Belanoff, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. **Exhibits 1-7,** attached hereto, are incorporated herein by reference.

2. I received an M.D. in 1992 from Columbia University, College of Physicians and Surgeons.

3. I am the inventor of the subject application and I am presently the CEO of Corcept Pharmaceuticals, Inc., the named assignee of the subject application. Corcept's primary mission is to provide improved medicine for psychiatric illnesses.

4. I have read and am familiar with the contents of the application. I understand that the Examiner has rejected the pending claims under §103 based upon her belief that one of skill reading the prior art of Schatzberg (U.S. Pat. No. 6,150,349) in view of Ademmer and/or Dieterich and Shimizu would have a reasonable expectation that patients with psychosis induced by IFN-α would be treatable with glucocorticoid receptor antagonist [GRA].

5. In the previous Office Action mailed on May 7, 2008, the Examiner based her rejections upon the combination of Schatzberg and Ademmer or Dieterich. According to the Examiner, Schatzberg taught that glucocorticoid receptor antagonists [GRAs] can be used to treat psychosis due to glucocorticoid dysregulation, and Ademmer and Dieterich disclose psychotic episodes in persons taking IFN-α for chronic conditions. It was explained in our response mailed on August 22, 2008 that the combination of references failed link IFN-α induced psychosis with glucocorticoid dysregulation.

In the final office action the Examiner cited to Shimizu as teaching that IFN-α can elevate cortisol. The obviousness rejection was maintained.

6. Shimizu by itself does not tell the full story of the impact of IFN-α on the hypothalamic pituitary adrenal axis [HPA]. Shimizu is following up on the earlier work of Roosth *et al.* in 1986 **(Exhibit 1)** where they report that following injections of IFN-α cortisol levels increase but return to normal within 24 hours. On page 315, the authors note that the phenomenon was transient. There was thought that the elevation in cortisol might be due to the transient fever that often accompanies the administration of IFN-α (see table 3).

In 1993, Muller *et al.* **(Exhibit 2)** looked at the mechanism of action for the reports of IFN-α elevation of cortisol and ACTH. They emphasize the possibility that

fever might be the cause (page 499, 1st column). They note in the first sentence of the abstract on page 499, that the observed effect is "short term" and these studies were confined to measuring cortisol in the first 24 hours after administration. The results of Muller confirm the results of Roosth and Shimizu. The IFN-α induced cortisol elevation is transient with maximal levels arising after 5.8 hours (see table 2 on page 502). They also concluded that temperature elevations were not likely the cause of the transient elevation.

IFN-α therapy is often used as a long term therapy for chronic conditions. In 1993, Gisslinger *et al.* (**Exhibit 3**) looked at patients treated with IFN-α for three weeks and concluded that the transient elevation of cortisol was actually temporary and after 3 weeks, the cortisol elevation disappeared. Gisslinger called it "IFN-α –induced adaptive changes in the HPA" (see abstract). They wrote in their abstract, " After three weeks of IFN-α therapy, no significant stimulation of the HPA was observed."

7. Having demonstrated that the Shimizu disclosure of IFN-α stimulated HPA is reporting on a temporary phenomenon and that disappears after 3 weeks, the remaining question is whether the IFN-α –induced psychosis is present within this 3 week window. It is not. IFN-α-induced psychosis is observed in <1.0% of the patients taking the drug and arises only after months of therapy. Thus, our method of treatment claims address a disease that is clearly outside the 3 week window where IFN-α elevates cortisol.

Evidence that IFN-α –induced psychosis arises after months of IFN-α therapy can be found in the literature. See **Exhibits 4-7:** Bozikas 2001 (**11 months** of continuous treatment); Shafer 2000 (**4 months**), Taman 2003 (**5 months**) and Pabaney 2007 (**4 months**).

8. It is my opinion that one of skill reading Schatzberg, Ademman, Dieterich and Shimizu **in view of Gisslinger and the reports of exhibits 4-7** would not be motivated to consider GRAs as an effective therapy for treating IFN-α –induced pyschosis. The combination of references clearly suggests away from my invention.

This Declarant has nothing further to say.

Dated: 3/10/09

Joseph Belanoff, M.D.

Attachment: Exhibits 1-7

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